

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
12 May 2005 (12.05.2005)

PCT

(10) International Publication Number
WO 2005/041750 A2

(51) International Patent Classification⁷: **A61B**
(21) International Application Number:
PCT/US2004/034619
(22) International Filing Date: 20 October 2004 (20.10.2004)
(25) Filing Language: English
(26) Publication Language: English
(30) Priority Data:
60/514,268 24 October 2003 (24.10.2003) US
(71) Applicant (for all designated States except US): **MERCK & CO., INC.** [US/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US).
(72) Inventor; and
(75) Inventor/Applicant (for US only): **CLARK, Janet** [US/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US).
(74) Common Representative: **MERCK & CO., INC.**; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— without international search report and to be republished upon receipt of that report

[Continued on next page]

(54) Title: METHOD FOR IDENTIFYING COMPOUNDS THAT AFFECT EXPRESSION OF TRYPTOPHAN HYDROXYLAASE ISOFORM 2

```
mTPH2: MOPAMMFSSKYWARRGLSLDSAVPEDHOLLGSLTONKAIKSEDKKSGKEPGKCDTTE
mTPH1: M.....I...EDNKENKEN.KDHSSE

mTPH2: SSKTAVVFLKNEVGGLVKALRLFOEKHVNMLHIESRRSRSSSEVEIFVDCCEGKTE
mTPH1: RGRVTLIFSLNEVGGLIKVLKIFQENHVSLLHIESRKSQRNSEFEIFVDCDTSREQ

*****

mTPH2: FNELTQLLKQTTIVTLNPPESIWTTEEEDLEVPWFPRKISELDRCSHRVLMYGTELD
mTPH1: LNDIFPLLKSHATVLSVDSPOQLTAKEDVMEIVPWFPKISDLDLCANRVLLYGSELD

mTPH2: ADHPGFKDNYRQRKYFVDVAMGYKYGQPIPRVEYTEEEIKTWGVFREL SKLYPTH
mTPH1: ADHPGFKDNYRQRKYFAELAMNYKHGDIPIKIEFTEEEIKTWGITFRELNKLYPTH

mTPH2: ACREYLKNIPLLLTKYCYREDNIPQLEDVSMFLKERSGFTVRPVAGYLSPRDFLAGLA
mTPH1: ACREYLRNPLLLSKYCYREDNIPQLEDVSNFLKERTGFSIRPVAGYLSPRDFLSGLA

mTPH2: YRVFHCQYVRHGSDDPLYTPEPDTCHELLGHVPLLADPKFAQFSOEIGLASLGASDED
mTPH1: FRVFHCQYVRHGSDDPLYTPEPDTCHELLGHVPLLAEPFAQFSOEIGLASLGASEET

*****

mTPH2: VQKLATCYFFTIEFGLCKQEQQLRAYGAGLLSSIGELKHALSDKACVKSFPDPTTCLQ
mTPH1: VQKLATCYFFTIEFGLCKQEQQLRVFGAGLLSSISELKHALSGHAKVKPFPDPTACKQ

mTPH2: ECLITTFQDAYFVSDSFEEAKEKMRDFAKSIIRPFVYFNRYTOSIEILKDRSIEV
mTPH1: ECLITTFQDAYFVSESEDAKEKMRFAKTVKRPFGKYNPYTQSVQVLRDTSITSA

*****

mTPH2: VQDLRSDLTNVCDALEKQNYLGI
mTPH1: MNELRYDLVLSDALARVTRNPSV
```

Light Text = Identity between sequences (68 %)
----- = TPH2a ISH probe
----- = TPH2b ISH probe
----- = TPH1-892 ISH probe
Underlined residues = TPH2c ISH probe
***** = Real-time RT-PCR amplicons
□ = Catalytic domain

(57) Abstract: A method for identifying analytes which directly or indirectly affect tryptophan hydroxylase isoform 2 (TPH2) expression is described. The method enables glucocorticoid receptor modulators and α -hydroxysteroid dehydrogenase type 1 (α -HSD1) inhibitors to be screened for central nervous system penetrance and activity by determining their ability to regulate expression of TPH2. The method is particularly useful for identifying analytes which suppress glucocorticoid disruption of central serotonergic neurotransmission in the brain.



For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.